matory reaction of the myocardium, a definition reemphasized by the criteria developed by Aretz and colleagues, which base the diagnosis on the histopathologic demonstration of coexisting myocyte necrosis and cellular infiltration.[9] Without denying the clinical value if not necessity of diagnostic standards such as the Dallas criteria, we wonder if our understanding of the biology of the cardiac effects of viral infections and associated immune or autoimmune reactions may not be better served by keeping an open mind with regard to the morphologic and functional expressions of viral and immunologic effects on the heart. Viruses may also invade interstitial cells such as fibroblasts, as well as vascular smooth muscle cells. The effects of such involvement on cardiac function have hardly been explored, although recently the cytoskeleton has been given some attention in the pathogenesis of dilated cardiomyopathy.[10]

Such concepts might lead to surveys of patients with acute viral disease by means of radionuclide studies such as antimyosin scans,[11] along with noninvasive assessments of cardiac function such as echocardiograms and radioventriculograms, and with endomyocardial biopsies, with follow-up to determine the incidence of later evidence for dilated cardiomyopathy.

As a logical result of the increasing evidence for a role of the immune system in ongoing subacute and chronic myocardial inflammatory processes, immunosuppressive therapy has come into increasing clinical use, not only in patients with biopsy results positive for active myocarditis, but also in patients with dilated cardiomyopathy of recent onset. In view of the absence of proof of the effectiveness and the significant side effects of immunosuppressive agents, the controlled randomized trial described by O'Connell and Mason is of the utmost importance. The considerable differences in immunologic processes found in different strains of inbred mice,[6,7] however, suggest that immunosuppressive therapy with one agent may not be uniformly effective. It is hoped that the simultaneous study of indices of humoral and cellular immunopathogenetic factors will permit an analysis of the effect of immunosuppressive therapy in relation to subgroups of patients. It would be erroneous, however, to conclude that the immune system has only a deleterious effect on the myocardium in this disease. Studies of experimental viral infection in mice have shown that suppression of the immune system during the viremic phase of the infection may enhance myocardial replication of virus and myocardial damage.[12,13] Thus, immunosuppressive therapy should not be considered during the acute viremic phase of a viral myocarditis.

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REFERENCES

1. Wenger NK, Abelmann WH, Roberts WC: Myocarditis, chap 57, *In* Hurst JW (Ed): The Heart, Arteries and Veins, 6th Ed. New York, McGraw-Hill, 1986, pp 1158-1180
2. Abelmann WH: Viral myocarditis and its sequelae. Annu Rev Med 1973; 24:145-152
3. Miklozek CL, Kingsley EM, Crumpaker CS, et al: Serial cardiac function tests in myocarditis. Postgrad Med J 1986; 62:577-579
4. Kline IK, Saphir O: Chronic pernicious myocarditis. Am Heart J 1960; 59:681-697
5. Abelmann WH: Myocarditis as a cause of dilated cardiomyopathy, chap 13, *In* Engelmeier RS, O'Connell JB (Eds): Drug Therapy in Dilated Cardiomyopathy and Myocarditis. New York, Marcel Dekker, 1988, pp 221-231
6. Herskowitz A, Wolfgram LJ, Rose NR, et al: Coxsackievirus B3 murine myocarditis: A pathologic spectrum of myocarditis in genetically defined inbred strains. J Am Coll Cardiol 1987; 9:1311-1319
7. Kishimoto C, Kawai C, Abelmann WH: Immuno-genetic aspects of the pathogenesis of experimental viral myocarditis, *In* Kawai C, Abelmann WH (Eds): Pathogenesis of Myocarditis and Cardiomyopathy: Recent Experimental and Clinical Studies. Tokyo, University of Tokyo Press, 1987, pp 3-7
8. Gwathmey JK, Nakao S, Matsumori A, et al: Large animal model of viral myocarditis. Circulation 1986; 74(suppl II):II-163
9. Aretz HT, Billingham ME, Edwards WD, et al: Myocarditis: A histopathologic definition and classification. J Cardiovasc Pathol 1987; 1:3-14
10. Cohen-Gould L, Robinson TF, Factor SM: Intrinsic connective tissue abnormalities in the heart muscle of cardiomyopathic Syrian hamsters. Am J Pathol 1987; 127:327-334
11. Haber E, Yasuda T, Palacios IF, et al: Antimyosin scintigraphy in the diagnosis of acute myocarditis, *In* Kawai C, Abelmann WH (Eds): Pathogenesis of Myocarditis and Cardiomyopathy: Recent Experimental and Clinical Studies. Tokyo, University of Tokyo Press, 1987, pp 277-280
12. Monrad ES, Matsumori A, Murphy JC, et al: Therapy with cyclosporine in experimental murine myocarditis with encephalomyocarditis virus. Circulation 1986; 73:1058-1064
13. O'Connell JB, Reap EA, Robinson JA: The effects of cyclosporine on acute murine Coxsackie B3 myocarditis. Circulation 1986; 73:353-359

The Fetus as Patient

A GENERATION AGO the human fetus seemed a mystery, hidden within the walls of the uterus and far removed from the efforts of diagnostic and therapeutic medicine. This began to change in a significant way with the advent of amniocentesis in cases of Rh isoimmunization in the 1950s, followed by genetic amniocentesis in the 1960s to determine the fetal chromosomal status. By the 1970s, sonographic imaging of the fetus had matured to the point of providing detailed and clinically useful anatomic information within the womb. It could truly be said that the walls separating the physician from the fetus had crumbled and that during pregnancy there now were two patients calling on the skill and technology of modern medicine, the mother and her unborn baby.

The rapid progress in fetal medicine has been exciting to its practitioners and to most families who seek medical information about their unborn babies. As of the present, diagnostic efforts have greatly outstripped therapeutic ones on behalf of the fetus, however. This situation is not unexpected and parallels most other new areas in medicine. A future era of expanded fetal therapeutic options will stand rightfully on an established understanding of normal fetal development and physiology and the refined ability to make correct diagnoses.

A concomitant of rapid progress is a certain level of confusion in other areas of society, including the law, as to the meaning and implications of fetal medicine. Debates have sprung up about the existence and extent of a fetal right to medical intervention, about possible expected behaviors of a mother vis-à-vis her fetus, and about the means of resolution or adjudication if there seems to be a conflict between maternal (or paternal) and fetal interests. Controversy about elective abortion greatly complicates these questions. It is likely that we will have continued unrest surrounding these issues for quite some time.

The success of prenatal diagnosis has coincided with the willingness to go to the fetus—that is, to enter the womb for diagnostic testing. From the point of view of risks and complications to the fetus and pregnancy, it would be preferable to stay outside of the womb and make do with maternal blood and urine specimens, abdominal palpation and auscultation, or other innocuous examinations. With the exception of measurements of maternal serum α-fetoprotein concentrations, this safest approach has not yet been fruitful for the diagnosis of fetal disease. Even so, it is axiomatic that the least invasive modality of fetal examination be chosen consistent with being able to accomplish a desired diagnosis.

One can draw obvious parallels in the diagnostic ap-

proaches to the postnatal versus the prenatal patient. For imaging after birth we use our eyes, x-ray films, magnetic resonance, and sound waves. For imaging the fetus, sonography is the mainstay; it gives excellent definition of both surface and internal anatomy as well as certain behaviors or functions of the fetus such as urination, breathing, blood flow, and heart action. Magnetic resonance imaging of the fetus is in its infancy and transabdominal endoscopic (fetoscopic) visualization has limited use because of relatively high risks. Sonography, on the other hand, has thus far proved risk free. With continually improving quality, sonographic imaging has become indispensable for visualizing the fetus and, equally important, for guiding intrauterine tissue sampling and therapeutic efforts.

Blood and urine analyses are crucial diagnostic tests postnatally. Amniotic fluid substitutes to some extent for urine in utero because fetal urine is a major constituent in the second and third trimesters. The appearance of metabolic products in amniotic fluid is attenuated, however, because of the continuous dialysis that occurs in the placenta. Blood sampling from the umbilical cord provides small but adequate specimens for the measurement of plasma constituents and the study of cellular components. Access to the fetal blood stream has become important not only for diagnosis but also for initiating and observing therapeutic interventions. Intrauterine umbilical vein transfusions for severe anemia in the fetus are increasingly being guided by concurrent measurements of the fetal hematocrit.[1]

Tissue or cellular biopsy is another conspicuous modality for diagnosis in the postnatal patient. It, too, has its parallel in utero. In fact, except for anatomic definition by ultrasonography, cellular analyses have been the most often used diagnostic studies of the fetus. The emphasis on genetic definition of the fetus has called for chromosomal, DNA, and enzyme analyses and these, in turn, have required cells. Within the womb, however, there have been two convenient sources of cells apart from the fetal body proper. These are the cells suspended in amniotic fluid, obtained by amniocentesis, and cells from the placenta, obtained by chorionic villus biopsy. Cells from both sites contain the fetal genome and in most respects accurately reflect the fetal genetic status. Amniocentesis in the second trimester has been used widely for two decades with a small risk of miscarriage, estimated at 0.5% to 1% or less.[2,3] Chorionic villus sampling in the first trimester is the subject of current investigations; its attendant fetal loss rate appears to be only slightly higher, less than 1%, than that of amniocentesis.[4]

Fetal tissue sampling directly from the fetal body is also done. Blood sampling is the most important technique and gives access to erythrocytes, leukocytes, and platelets. Skin biopsy and liver biopsy have also been developed but are used infrequently because diagnostic questions rarely require those tissues and the risks of the procedures remain relatively high.

Golbus and co-workers elsewhere in this issue report their long experience with fetal tissue sampling. The major experience is with fetal blood sampling, and they chronicle the evolution of the sampling technique and the changing indications for the procedure. The two important technical advances were the switch from using the vessels on the chorionic plate of the placenta as a source of blood to those in the umbilical cord when the fetoscope was being used[5] and, subsequently, the abandonment of the fetoscope for a percutaneous introduction of the blood sampling needle during ultrasound imaging.[6]

The changing indications for diagnostic fetal blood sampling, apart from its use in conjunction with fetal therapy, reflect changing diagnostic technologies and different diagnostic questions. Today there is a rapidly increasing ability to diagnose genetic disorders by the analysis of DNA, rather than having to depend on gene products or altered metabolism. The fetal genome is present in amniocytes and chorionic villus cells; genes can be studied whether or not their products are synthesized in those cells. Thus, we no longer need blood to analyze the hemoglobin molecule or measure clotting factors. Instead, we can analyze the globin genes or the genes for clotting factors.

An increasing indication for fetal tissue is the clarification or refinement of chromosomal diagnoses. Chromosomal mosaicism occurs in both amniocytes and chorionic villus cells at a low rate. At times cells directly from the fetus are desired to improve the interpretation. Mosaicism can never be completely excluded, however, so a level of uncertainty always remains. Also, for a few chromosomal trisomy disorders, it appears that blood cells are unlikely to express mosaicism even though it is present in other tissues; this is probably true for trisomy 7 and trisomy 20. Further investigation of mosaicism with these trisomy defects might call for a skin biopsy instead of, or in addition to, blood sampling.

In recent years it has become possible to look to fetal blood for evidence of an active infection. The immune response of the fetus, hematologic evidence of infection, and liver chemistries have all proved useful in this regard. Experience with both rubella and toxoplasmosis has been encouraging as to the accuracy of diagnosis.

When we accept the unborn baby as a patient, we must also look to the safety of our diagnostic and therapeutic interventions. As reported by Golbus and associates, the risk of fetal blood sampling has dropped as advances have been made in the sampling technique. In the hands of experienced perinatologists, the risk of fetal loss is approaching the risk with amniocentesis. Risks associated with several therapies are also low. These include the use of high-dose vitamin therapy through the mother in a few rare inborn errors of metabolism, administering cardioactive drugs, and transfusion through the umbilical vessels. Less safe or less efficacious have been attempts at the placement of shunts into the fetal body or other surgical interventions. Safety continues to improve, though, in all areas of fetal medicine even as the range of possible diagnoses and therapies expands rapidly. The needs of our unborn patients have become more clearly known to us, and concerted efforts to meet those needs continue to be forthcoming.

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1. Grannum PAT, Copel JA: Prevention of Rh isoimmunization and treatment of the compromised fetus. Semin Perinatol 1988; 12:324-335
2. Elias S, Simpson JL: Amniocentesis, *In* Milunsky A (Ed), Genetic Disorders and the Fetus, 2nd Ed. New York, Plenum Press, 1986, pp 44-48
3. Tabor A, Philip J, Madsen M, et al: Randomized controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet 1986; 1:1287-1293
4. Rhoads GG, Jackson LG, Schlesselman SE, et al: The safety and efficacy of chorionic villus sampling—Initial findings from the United States collaborative study. N Engl J Med 1989; 320:609-617
5. Rodeck CH, Campbell S: Umbilical-cord insertion as source of pure fetal blood for prenatal diagnosis. Lancet 1979; 1:1244-1245
6. Daffos F, Capella-Pavlovsky M, Forestier F: Fetal blood sampling during pregnancy with use of a needle guided by ultrasound: A study of 606 consecutive cases. Am J Obstet Gynecol 1985; 153:655-660